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April 12, 2005

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APPLICATION NUMBER: *60/544,970*
FILING DATE: *February 12, 2004*

DK/05/75

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Lars Ole	Lyngso	Bagsværd, Denmark

Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

METHOD FOR THE PREPARATION OF INTERMEDIATES WHICH MAY BE USED FOR THE PREPARATION OF ESCITALOPRAM

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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OR

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ENCLOSED APPLICATION PARTS (*check all that apply*)

[x] Specification *Number of Pages* 30
[ ] Drawing(s) *Number of Sheets*
[x] Application Data Sheet. See 37 CFR 1.76
[ ] CD(s), Number
[ ] Other (specify):

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

[ ] Applicant claims small entity status. See 37 CFR 1.27.
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FILING FEE AMOUNT ($): 160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

[x] No [ ] Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____

TYPED OR PRINTED NAME Jay P. Lessler

TELEPHONE (212) 527-7765

Date February 12, 2004

REGISTRATION NO. *(if appropriate)* 41,151

Docket Number: 05432/0200888-US0

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003, Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 160.00

Complete if Known	
Application Number	Not Yet Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Lars O. Lyngso
Examiner Name	Not Yet Assigned
Art Unit	N/A
Attorney Docket No.	05432/0200888-US0

METHOD OF PAYMENT *(check all that apply)*

☒ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

Deposit Account Number: 04-0100

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1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	160.00

SUBTOTAL (1) ($) 160.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below	=	Fee Paid
Total Claims	-** =		x		=	
Independent Claims	-** =		x		=	
Multiple Dependent					=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 0.00

SUBMITTED BY

(Complete *(if applicable)*)

Name (Print/Type)	Jay P. Lessler	*Registration No. (Attorney/Agent)*	41,151	*Telephone*	(212) 527-7770
Signature				*Date*	February 12, 2004

Express Mail Label No. Dated: _____

Application No. (if known):

Attorney Docket No.: 05432/0200888-US0

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Provisional Patent Application Transmittal (1 page)
Fee Transmittal (1 page)
Application Data Sheet (2 pages)
Specification, Claims and Abstract (30 pages)
Check No. 4145 in the amount of $160.00

Method for the separation of intermediates which may be used for the preparation of escitalopram

The present invention relates to a novel method for the preparation of optically active intermediates useful for the preparation of escitalopram.

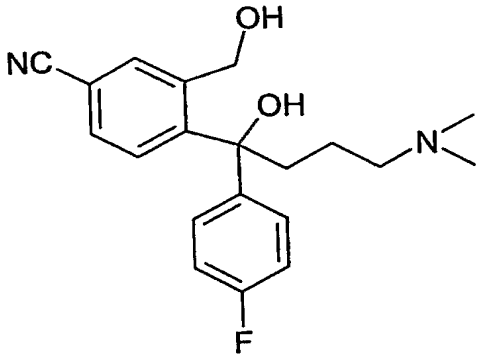
Background of the invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years.

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication i.a. outlines a process for preparation of citalopram from the corresponding 5-bromo-derivative by reaction with cuprous cyanide in a suitable solvent and by alkylation of 5-bromo-phtalane.

US Patent No 4,943,590 corresponding to EP-B1-347 066 describes two processes for the preparation of escitalopram (S-enantiomer of citalopram). Both processes use the racemic diol having the formula



(I)

as starting material. According to the first process, the diol of formula (I) is reacted with an enantiomerically pure acid derivative, such as (+) or (-)-α-methoxy-α-trifluoromethyl-phenylacetyl

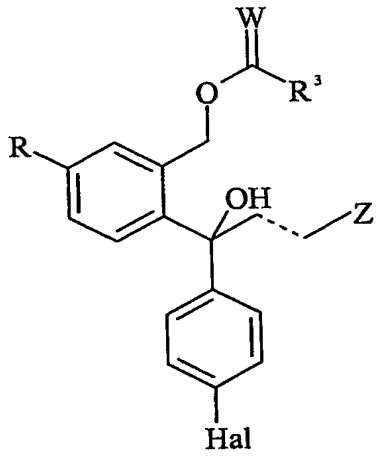
chloride to form a mixture of diastereomeric esters, which are separated by HPLC or fractional crystallization, whereupon the ester with the correct stereochemistry is enantioselectively converted into escitalopram. According to the second process, the diol of formula (II) is separated into the enantiomers by stereoselective crystallization with an enantiomerically pure acid such as (+)-di-*p*-toluoyltartaric acid, whereupon the S-enantiomer of the diol of the formula (A) is enantioselectively converted to escitalopram.

Escitalopram has now been developed as an antidepressant. Hence, there is a desire for an improved method for preparation of escitalopram.

It has been found that the S-enantiomer of the diol of formula (I) above as well as acylated derivatives thereof may be prepared by selective enzymatic acylation of the primary hydroxyl group in the racemic diol to obtain S-diol or an acylated derivative thereof with high optical purity and further that the enantiomers obtained may be effectively separated by reaction of the diol with a compound which form a derivative of the diol containing a carboxylic acid group. The derivative formed precipitates once it is formed and may easily be separated from the reaction mixture.

The invention

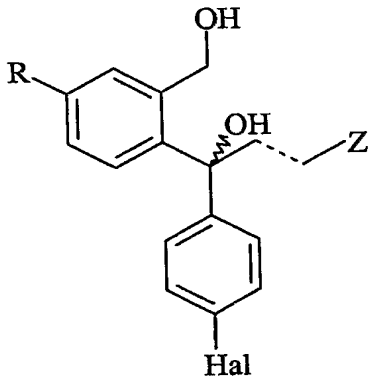
Accordingly, the present invention relates to a method for the isolation and purification of a compound having the formula



(IV)

wherein R is cyano or a group which may be converted to a cyano group, the dotted line represents a double or single bond, Hal is halogen, Z is a dimethylaminomethyl group or Z is a group which may be converted to a dimethylaminomethyl group, W is O or S and R^3 is -Y-R^1 wherein Y is a bond, O, S or NH and R^1 is C_{1-10}-alkyl, C_{2-10}-alkenyl or C_{2-10}-alkynyl all of which may optionally be substituted with one or more substituents selected from C_{1-10}-alkoxy, C_{1-10}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-10}-alkylamino, di-(C_{1-10}-alkyl)amino, aryl, aryloxy, arylthio and heteroaryl, or R^1 is aryl, wherein any of the the aryl and heteroaryl groups may optionally be substituted one or more times with substituents selected from C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{2-10}-alkynyl, C_{1-10}-alkoxy, C_{1-10}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-10}-alkylamino and di-(C_{1-10}-alkyl)amino, or a salt thereof

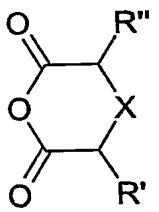
and/or a diol of formula



(II)

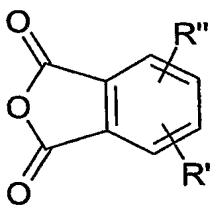
wherein R, Z, Hal and the dotted line are as defined above, or a salt thereof, from a mixture containing the compound of formula (IV) and the diol of formula (II), which comprises:

a) reacting said mixture containing the compound of formula (IV) and the diol of formula (II) with a cyclic anhydride or imide of formula



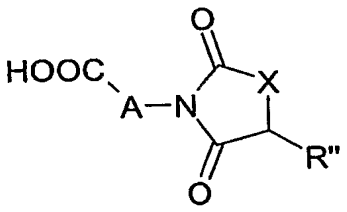
(Ia)

or



(Ib)

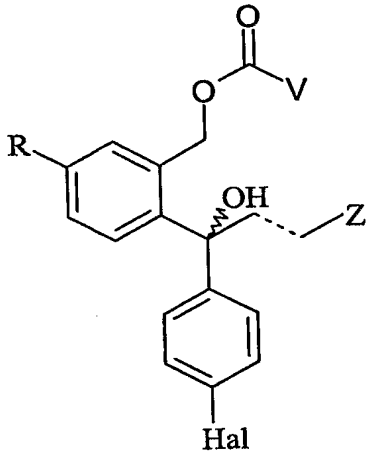
or



(Ic)

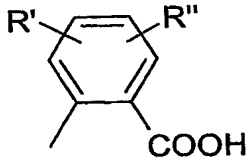
wherein X is $-(CHR'''')_n-$, wherein n is 0-2; and R', R" and R'''' are independently selected from hydrogen or C_{1-6}-alkyl, and A is C_{1-6}-alkylen, phenylen, or naphthylen wherein the C_{1-6}-alkylen, phenylen, or naphthylen groups may optionally be substituted with one or more times with C_{1-6}-alkyl;

to form a mixture of the compound of formula (IV) and an ester having the formula



(V)

wherein R, Z and Hal is as defined above and V is –CHR'-X-CR"-COOH, -X-CHR"-CO- NH-A-COOH, - CHR''-X-CO-NH-A-COOH or



wherein R', R", X and A are as defined above;

b) allowing the acid of formula (V) to precipitate from the reaction mixture; and

c) separating the precipitate of the compound of formula (V) from the reaction mixture, optionally followed by isolation of the compound of formula (IV) or a salt thereof from the reaction mixture.

According to one particular embodiment of the invention, one enantiomer of formula (II) is separated from a compound of formula (IV) in the form of the other enantiomer.

According to one embodiment of the invention the S-enantiomer of the compound of formula (V) is separated from the R-enantiomer of the acyl derivatitive of formula (IV).

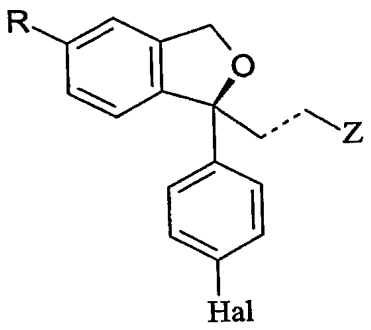
According to another embodiment, the S-enantiomer of the acyl derivative of formula (IV) is separated from the R-enantiomer of the compound of formula (V).

According to one specific embodiment of the invention , the reagent used is a compound of formula (Ia), suitably succinic anhydrid or glutaric anhydrid.

According to another specific embodiment, the reagent used is a compound of formula (Ib), suitably phatalic acid anhydride.

According to a third embodiment of the invention the reagent is an imide is a compound of Formula (Ic), suitably N-phenyl-succinimide substituted in the phenyl ring with a carboxy group.

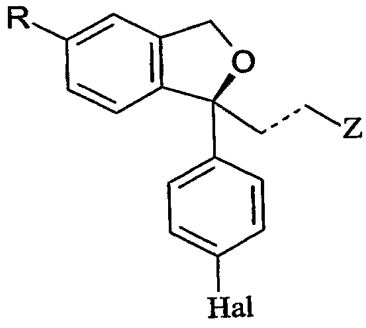
According to a further embodiment of the invention the R group in the compound of formula (V) in obtained in the form of the S-enantiomer is optionally converted to cyano, the Z group in the compound of formula V obtained is optionally converted to a dimethylaminomethyl group, Hal is optionally converted to fluoro and /or a dotted line representing a double bond is optionally converted to a single bond, in either order, followed by conversion of the compound of formula (V) to escitalopram or a derivative thereof having the formula



(VI)

wherein R, Z and Hal is as defined above by treatment with a base, optiona optionally followed by, in either order, conversion of the group R to a cyano group, conversion of the group Z to a dimethylaminomethyl group, conversion of Hal to fluoro, and conversion of a dotted line representing a double bond to a single bond; optionally followed by conversion of escitalopram or a derivative of formula (VI) to a salt thereof.

According to another embodiment of the invention the R group in the compound of formula (IV) the obtained in the form of the S-enantiomer is optionally converted to cyano, the Z group in the compound of formula IV obtained is optionally converted to a dimethylaminomethyl group, Hal is optionally converted to fluoro and /or a dotted line representing a double bond is optionally converted to a single bond, in either order, followed by conversion of the compound of formula (IV) to escitalopram or a derivative thereof



(VI)

wherein R, Z and Hal is as defined above by treatment with a base, optionally followed by, in either order, conversion of the group R to a cyano group, conversion of the group Z to a dimethylaminomethyl group, conversion of Hal to fluoro, and conversion of a dotted line representing a double bond to a single bond; optionally followed by conversion of escitalopram or a derivative of formula (VI) to a salt thereof.

According to the most preferred embodiment of the invention, a mixture of the compound of formula (II) and (IV) wherein R is cyano, the dotted line is a single bond, Z is dimethylaminomethyl, Hal is fluoro, R^3 is $-O-CH_2-CH_2-CH_3$ is reacted with amide of formula (Ia) wherein X is $-(CH_2)_{0-1}$ to form a mixture of the corresponding S-enantiomer of formula (V) and the R-enantiomer of formula (IV). The isolated compound of formula (V) is then treated with NaH to form the compound of formula (VI).

The mixture of formula (II) and (IV) used as stating material is preferably prepared by enzymatic acylation of a compound of formula II wherein R is cyano, the dotted line is a single bond, Z is dimethylaminomethyl, Hal is fluoro, using vinylbutyrate as acylating agent and the enzyme Candida antartica lipase B.

Detailed description of the invention

When used in connection with the compounds of formula (II), (IV), (V) and (VI), the terms "enantiomer", "R-enantiomer", "S-enantiomer", "R-form", "S-form", "R-diol" and "S-diol" refer to the orientation of the groups around the carbon atom to which the 4-Hal-phenyl group is attached.

As used herein, the term C_{1-10}-alkyl refers to a branched or unbranched alkyl group having from one to ten carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, pentyl, hexyl and heptyl. C_{1-6}-alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, pentyl and hexyl. C_{1-4}-alkyl refers to a branched or unbranched alkyl group having from one to four carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl. C_{1-3}-alkyl refers to a branched or unbranched alkyl group having from one to three carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl.

Similarly, C_{2-10}-alkenyl and C_{2-10}-alkynyl designate branched or unbranched alkenyl and alkynyl groups, respectively, having from two to ten carbon atoms, including one double bond and one triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl. C_{2-6}-alkenyl and C_{2-6}-alkynyl designate branched or unbranched alkenyl and alkynyl groups,

respectively, having from two to six carbon atoms, including one double bond and one triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl. C_{2-4}-alkenyl and C_{2-4}-alkynyl designate branched or unbranched alkenyl and alkynyl groups, respectively, having from two to four carbon atoms, including one double bond and one triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl. C_{2-3}-alkenyl and C_{2-3}-alkynyl designate branched or unbranched alkenyl and alkynyl groups, respectively, having from two to three carbon atoms, including one double bond and one triple bond respectively, such as ethenyl, propenyl, ethynyl and propynyl.

The terms C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylamino and di-(C_{1-10}-alkyl)amino etc. designate such groups in which the alkyl group is C_{1-10} alkyl as defined above. The terms C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino and di-(C_{1-6}-alkyl)amino etc. designate such groups in which the alkyl group is C_{1-6} alkyl as defined above. The terms C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino and di-(C_{1-4}-alkyl)amino etc. designate such groups in which the alkyl group is C_{1-4} alkyl as defined above. The terms C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylamino and di-(C_{1-3}-alkyl)amino etc. designate such groups in which the alkyl group is C_{1-3} alkyl as defined above.

Halogen means fluoro, chloro, bromo or iodo.

In a preferred embodiment of the invention R is halogen or cyano, most preferred cyano.

In a further preferred embodiment of the invention Hal is fluoro,

In a further embodiment of the invention, the dotted line in formula (II), (IV) and (V) is a single bond.

In still a further embodiment Z is dimethylaminomethyl or a group that may be converted to dimethylaminomethyl. In a preferred embodiment Z is dimethylaminomethyl.

Most preferred, Hal is fluoro, R is cyano, the dotted line is a single bond and Z is dimethylaminomethyl.

According to one embodiment of the invention, Y in the compound of formula (IV) is O or S.

According to another embodiment of the invention, Y in the compound of formula (IV) is NH.

However, according to a preferred embodiment of the invention, Y in the compound of formula (IV) is a bond.

Suitably, the substituent R^1 in the compound of formula (IV) as defined in any of the embodiments above, is as follows: R^1 is C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl all of which may optionally be substituted one or more times with substituents selected from C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-4}-alkylamino and di-(C_{1-6}-alkyl)amino, more suitable R^1 is C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl all of which may optionally be substituted one or more times with substituents selected from C_{1-4}-alkoxy, C_{1-4}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-4}-alkylamino and di-(C_{1-4}-alkyl)amino, preferebly R^1 is C_{1-3}-alkyl, C_{2-3}-alkenyl or C_{2-3}-alkynyl all of which may optionally be substituted one or more times with C_{1-3}-alkoxy, C_{1-3}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-3}-alkylamino and di-(C_{1-3}-alkyl)amino, more preferred R^1 is C_{1-3}-alkyl, C_{2-3}-alkenyl or C_{2-3}-alkynyl, and more suitable R^1 is C_{1-3}-alkyl, in particular unbranched C_{1-3}-alkyl, such as methyl, ethyl or propyl

The present invention is particularly useful for separation of compounds of formula (II) in the form of the S- or the R-enantiomer and the compound of formula (IV) in the form of the opposite enantiomer obtained by enzymatic resolution according to the processes described in WO application No. PCT/DK/ 0300537.

Thus, according an embodiment of the invention the mixture of a compound of formula (II) and (IV) used in the process is prepared by selective enzymatic acylation or selective enzymatic deacylation.

A particular advantage of the present invention is that following formation, the compound of formula (V) precipitates from the reaction mixture and is thereafter easily isolated.

Another particular advantage of the present invention is that (depending on the particular reagent of formula (Ia) –(Ic) used) it results in the separation and isolation of a product which may be ring closed directly to form escitalopram by treatment with a base.

The reaction of the mixture of a compound of formula (II) in the form of one enantiomer with a compound of formula (Ia), (Ib) or (Ic) may be carried out in an inert organic solvent, such as tetrahydofuran, preferably a solvent in which the acid of formula (V) form a precipitate an in an amount of the particular solvent where the acid of formula (V) form a precipitate. Suitable solvents may be identified by the skilled person.

Alternatively the reaction is performed in a solvent from which the acid of formula (V) does not form a precipitate and an anti-solvent is added after formation of the compound of formula (V).

The reaction may suitably be carried out at or around room temperature (25 °C).

The compound of formula V is suitably separated from the compound of formula (IV) by filtration or decanting, or by any other suitable way of separating a solid form a liquid.

When the compound of formula V which is isolated as an S-enantiomer it may be ring closed directly by treatment with a base in a suitable organic solvent.

Enantioselective ring-closure of an S-enantiomer of formula (V) to form escitalopram or another compound of formula (VI) may suitably be carried out by treatment of the compound of formula (V) with a base such as $KOC(CH_3)_3$ and other alkoxides, NaH and other hydrides, triethylamine, ethyldiisopropylamine or pyridine, at low temperatures in an inert organic solvent, such as tetrahydrofuran, toluene, DMSO, DMF, t-butyl methyl ether, dimethoxyethane, dimethoxymethane, dioxane, acetonitrile or dichloromethane. This process is described in US patent No. 4,943,590.

In the same way, a compound of formula (IV) in the form of the S-enantiomer and separated from the reaction mixture, may be subjected to ring closure by treatment with a base.

In some cases, it may be advantageous to exchange the $-W-R^3$ group in the compound of formula IV or the –CO-V group in the compound of formula (V) for a more labile group, before ring closure is carried out. Such labile groups (leaving groups) could typically be a group selected from methanesulfonyloxy, *p*-toluenesulfonyloxy, 10-camphorsulfonyloxy, trifluoroacetyloxy and trifluoromethanesulfonyloxy or halogen.

Typically, the compound of formula (IV) or (V) is then subjected to hydrolysis to form the compound of formula (II) with aquesous base, such as NaOH, KOH or LiOH in water or alcohol or a mixture thereof and then reacted with an activated leaving group, such as for example mesylchloride or tosylchloride in an organic solvent in the presence of an organic base.

Preferably, the substituent V in the compound of formula (V), is a substituent which enable direct ring closure of the compund of formula V by treatment with a base. Most preferred, V is $-CH_2-CH_2-COOH$ or $-CH_2-CH_2-CH_2-COOH$.

The optical purity of the escitalopram product may have to be improved after ring closure. Improvement of the optical purity may be obtained by chromatography on a chiral stationary phase or by crystallisation of racemic citalopram base or a salt thereof according to the methods described in WO 03/000672.

The R-enantiomer of the compounds of formula (V) and (IV) obtained according to the invention may be used to prepare racemic citalopram and escitalopram by ring closure in acidic environment according to the method described in WO 03/000672. Suitable acids for carrying out acidic ring closure are mineral acid, a carboxylic acid, a sulfonic acid or sulfonic acid derivative, more suitable H_2SO_4 or H_3PO_4.

The starting mixture used for the separation method according to the invention may be prepared by enzymatic acylation or deacylation using a hydrolase, such as a lipase, an esterase, an acylase or a protease, as described in WO application No. PCT/DK/ 0300537.

It has been found that enzymatic acylation according to the invention may be carried out using Novozyme®435, from Candida antartica, LipoZyme™ TL IM from Thermomyces lanuginosus

both available from the company Novozymes A/S or Lipoprotein Lipase pseudomonas sp. (isolated from Pseudomonas Cepacia and obtained from Fluka), and particularly good results have been found when using Novozyme 435, from Candida antartica or Lipoprotein Lipase pseudomonas sp.

The "enzyme" or "hydrolase" may be immobilized as the enzyme itself or as a cell body by known techniques, and may be used in immobilized form. The immobilization may be carried out by methods known to the person skilled in the art, such methods include, for example carrier bonding, cross linking, encapsulation and the like. Thus, the hydrolase may be used in the form of an immobilized enzyme or Cross-Linked Enzyme Crystal (CLEC) enzymes.

The above mentioned enzymes may also be used in the form of cultured products containing the enzyme, such as culture fluid containing a cell body, or a cultured cell body, processed product of the cultured product and any immobilized forms of these enzymes/cultured products.

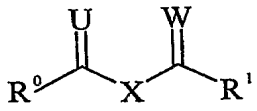
Mutants, variants or any equivalents of the above specifically mentioned enzymes, which are capable of performing the selective acylation or deacylation may also be used. The variants or equivalents thereof may be isolated from various strains of Pseudomonas, Candida or Thermomyces, or any other source, or they may be prepared by mutation of the DNA encoding the above mentioned enzymes leading to variations in the amino acid composition of the enzyme. Suitable the mutants or variants of the above mentioned enzymes are variants and mutants where single amino acids have been removed or replaced by other amino acids, and suitable the amino acid sequence of the variant or mutant is more than 60 % identical, preferably more than 80 % or most preferred more than 90 % identical to the above mentioned enzymes.
The preferred reaction conditions for enzymatic acylation/deacylation differ depending on the particular enzyme used, whether it is immobilised or not etc.

A suitable temperature for the reaction lies between 0-80 °C, more preferably between 20-60 °C, or more preferred between 30-50 °C.

The amount of enzyme to be used is not particularly restricted, but is usually 0.01-1.0, preferably 0.02-0.5 and more preferably 0.02-0.3, as weight ratio relative to substrate.

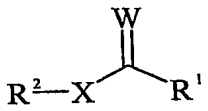
The reaction may be carried as a batch process or it may be carried out as a continous process. The enzyme may be used in a plurality of batches repeatedly or continuously. The reaction time is not particularly restricted, and will depend on the enzyme used and the scale and type production method (batch or continuous).

According to WO application No. PCT/DK/0300537 the acyalting agent used for the enzymatic acylation may be a reagent of formula



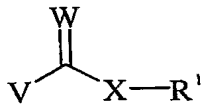
(IIIa)

or



(IIIb)

or



(IIIc)

or an isocyanate having the formula R^1-N=C=O or an isothiocyanate having the formula R^1-N=C=S;

wherein X is O or S; W is O or S; U is O or S, V is halogen;

R^0 is C_{1-10}-alkyl, C_{2-10}-alkenyl or C_{2-10}-alkynyl all of which may optionally be substituted one or more times with substituents selected from C_{1-10}-alkoxy, C_{1-10}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-10}-alkylamino, di-(C_{1-10}-alkyl)amino, aryl, aryloxy, arylthio and heteroaryl, or R^0 is aryl, wherein any of the aryl and heteroaryl groups may optionally be substituted one or more times with substituents selected from C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{2-10}-alkynyl, C_{1-10}-alkoxy, C_{1-10}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-10}-alkylamino and di-(C_{1-10}-alkyl)amino;

R^1 is as defined for R^0;
R^2 is as defined for R^0, or R^2 is a suitable leaving group; and
or R^0 and R^1 together form a chain of 3 to 5 carbon atoms;
provided that W and U is not S when X is S.

Preferably, U is O in the compound of formula (IIIa),

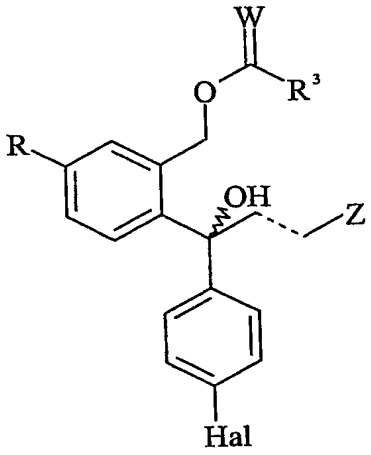
Preferably, W is s O in any of the above acylating agents.

Preferably, X is s O in any of the above acylating agents.

Preferably, R^1 and R^0 is C_{1-3}-alkyl, in particular unbranched C_{1-3}-alkyl, such as methyl, ethyl or propyl and preferably and R^2 is C_{1-3}-alkyl substituted one or more times with halogen or R^2 is C_{2-3}-alkenyl, and most preferred R^2 is C_{2-3}-alkenyl, such as vinyl.

A preferred acylating agent is vinyl butyrate.

Enzymatic deacylation may be carried using a compound of formula



(IV)

wherein R, Z, W, Hal, the dotted line and R^3 is as defined above, as starting material.

Suitably, R^1 is C_{1-10}-alkyl, preferably unbranched C_{1-10}-alkyl and more preferred R^1 is unbranched C_{4-10}-alkyl in the stating material used for enzymatic deacylation.

The selective enzymatic acylation is carried out under conditions substantially suppressing hydrolysis. Hydrolysis, which is the reverse reaction of the acylation reaction, takes place if water is present in the reaction system.

Thus, selective enzymatic acylation is preferably carried out in a water-free organic solvent or almost anhydrous organic solvent (enzymes normally require the presence of some water to be

active). The percentage of water allowed in a particular reaction system, may be determined by a person skilled in the art.

The organic solvent which may be used for the acylation reaction, is not particularly important as long as it does not deactivate the enzyme used. Suitable solvents include hydrocarbons such as hexane, heptane, benzene and toluene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, 1,4-dioxane, tert-butyl methyl ether and dimethoxyethane; ketones such as acetone, diethyl ketone, butanon, and methyl ethyl ketone; esters such as methyl acetate, ethyl acetate, ethyl butyrate, vinyl butyrate and ethyl benzoate; halogenated hydrocarbons such as methylene chloride, chloroform and 1,1,1-trichloroethane; seconday and tertiary alcohols, such as tert-butanol; nitrogen-containing solvents such as dimethylformamide, acetoamide, formamide, acetonitrile and propionitrile; and aprotic polar solvents such as dimethylsulfoxide, N-methylpyrrolidone and hexamethylphosphorous triamide.

Among them, hydrocarbons such as hexane, heptane, benzene and toluene, ethers such as diethyl ether, diisopropyl ether, 1,4-dioxane and tert-butyl methyl ether and esters such as vinyl butyrate, are preferred. For one enzymes the most preferred solvents may be aromatic hydrocarbons such as benzene or toluene and ethers, most preferred toluene and for another enzyme the most preferred solvents may be ethers such as 1,4-dioxane. The above solvents may be used singly or in a combination of two or more solvents.

The concentration of racemic diol of formula (II) and acylating agent should not be too high as a high concentration of reagents in the solvent may lead to non-selective acylation of the racemic diol. Suitable the concentration of racemic diol and acylating reagent is each below 1,0 M, more suitable below 0,5 M, even more suitable below 0,2 M or even more suitable below 0,1 M. A person skilled in the art will be able to determine the optimal concentration of racemic diol and acylating agent.

Selective enzymatic deacylation is preferably carried out in water or a mixture of water and an organic solvent, suitable in presence of a buffer. The organic solvent which may be used in the reaction, is not particularly important as long as it does not deactivate the enzyme used. Suitable organic solvents are solvents miscible with water such as alcohols, acetonitrile, DMF, DMSO,

dioxane, DME and diglyme . The skilled person will be able to identify other suitable solvents. A person skilled in the art will be able to determine the optimal concentration of racemic compound of formula (IV) used in the reaction

The stereoselectivity of the enzyme used, may be increased by carrying out the acylation or deacylation in presence of an organic acid and /or an organic base.

In particular the enzymatic acylation or enzymatic deacylation is carried out in the presence of an organic acid, suitable an organic carboxylic acid.

Suitable the above mentioned organic acid is an aromatic carboxylic acid or an aliphatic carboxylic acid.

Suitable organic acids which may be used in the reaction, are, alkyl carboxylic acids, cycloalkylcarboxylic acids, cycloalkylalkylcarboxylic acids, optionally substituted phenyl-alkylcarboxylic acids and optionally substituted phenylcarboxylic acids. Suitable aliphatic carboxylic acids, are carboxylic acids such as formic acid, acetic acid, propionic acid, n-butyric acid, iso-butyric acid, 2-ethylbutyric acid, n-valeric acid, iso-valeric acid, pivalic acid, n-caproic acid, iso-caproic acid, decanoic acid, crotonic acid, palmitic acid, cyclopentanecarboxylic acid, cyclohexanecarboxylic acid, phenyl-C_{1-4}-alkylcarboxylic acids such as 3-phenylpropionic acid, 4-phenylbutyric acid, oxalic acid, malonic acid and tartaric acid. Suitable aromatic carboxylic acids, includes acids such as benzoic acid, p-chlorobenzoic acid, p-nitrobenzoic acid, p-methoxybenzoic acid, p-toluic acid, o-toluic acid, m-toluic acid, naphthoic acid, phthalic acid and terephthalic acid, salicylic acid, hydrocinnamic acid for instance.

Preferably, the organic acid used to improve stereoseleselectivity of the enzyme is selected from n-propionic acid, iso-propionic acid, n-butyric acid, iso-butyric acid, iso-valeric acid, 2-ethylbutyric acid, crotonic acid, palmitic acid, cyclohexanecarboxylic acid, pivalic acid, benzoic acid and *p*-toluic acid, salicylic acid and 3-phenylpropionic acid. Most preferred, the carboxylic acid used is pivalic acid.

The amount of the organic acid to be used is not particularly restricted, but the molar ratio relative to a substrate is usually 0.1 to 10, preferably 1.0 to 3.0, and more preferably 1.0 to 2.0.

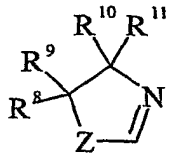
Alternatively, a tertiary amine may be used to improve selectivity of the enzyme, either alone or together with any of the above mentioned organic acid. As suitable organic base there may be mentioned, triethyl amine, pyridine, 4-dimethylaminopyridine and pyridine is preferred. Suitable combinations of organic acid and organic base are benzoic acid and pyridine for example.

The amount of the tertiary amine to be used is not particularly restricted, but the molar ratio relative to a substrate is usually 0.5 to 3.0, and preferably 0.5 to 2.0.

As mentioned above, the group R means cyano or any other group which may be converted to a cyano group.

Groups which may be converted to a cyano group include halogen such as chloro, bromo, iodo or fluoro, preferably chloro or bromo.

Other groups which may be converted to cyano include CF_3-$(CF_2)_n$-SO_2-O- , wherein n is 0-8, -OH, -CHO, -CH_2OH, -CH_2NH_2, -CH_2NO_2, -CH_2Cl, -CH_2Br, -CH_3, -NHR^5, -CHNOH, -$COOR^6$, -$CONR^6R^7$ wherein R^5 is hydrogen or C_{1-6} alkylcarbonyl, and R^6 and R^7 are selected from hydrogen, optionally substituted C_{1-6} alkyl, aryl-C_{1-6} alkyl or aryl and, a group of formula



(VII)

wherein Z is O or S; $R^8 - R^9$ are each independently selected from hydrogen and C_{1-6} alkyl or R^8 and R^9 together form a C_{2-5} alkylene chain thereby forming a spiro ring; R^{10} is selected from hydrogen and C_{1-6} alkyl, R^{11} is selected from hydrogen, C_{1-6} alkyl, a carboxy group or a precursor group therefore, or R^{10} and R^{11} together form a C_{2-5} alkylene chain thereby forming a spiro ring.

When R is halogen, in particular bromo or chloro, conversion to a cyano may be carried out as described in US 4,136,193, WO 00/13648, WO 00/11926 and WO 01/02383.

According to US 4,136,193 conversion of a bromo group to a cyano group, is carried out by reaction with CuCN.

WO 00/13648 and WO 00/11926 describe the conversion of a halogen or a triflate group to a cyano group by cyanation with a cyanide source in presence of a Pd or Ni catalyst.

Compounds wherein the group R is a group of formula (VII) may be converted to the corresponding cyano compound by methods analogous to those described in WO 00/23431.

Compounds wherein R is OH, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NO_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_3$ or any of the groups above, may be converted to the corresponding cyano compounds by methods analogous to those described in WO 01/68632.

Racemic compounds of formula (II) may be prepared by the methods described in the above mentioned patents or by the alkylation method described in US patent No. 4.136.193 or the double grignard reaction described in EP 171 943 or by analogous methods. Racemic compounds of formula (IV) may be prepared from racemic compounds of formula (II) by non-selective acylation using anhydrides, esters, carbonates, isocyanates or isothiocyanates as defined by formulas (IIIa), (IIIb), (IIIc), R^1-N=C=O and R^1-N=C=S above.

In some cases the racemic compound of formula (II) may be available in the form of an acid addition salt, such as the sulphate salt, and in this case a free base of the compound of formula (II) may be obtained by treating the salt with a base in a mixture or water and an organic solvent, to transfer the compound of formula (II) into the organic phase.

Preferably, R is cyano. If R is not cyano, conversion of the group R to a cyano group is suitably carried out after ringclosure to form a compound of formula (V).

Preferably, Hal is fluoro. If Hal is not fluoro, conversion of the group Hal to a fluoro is suitably carried out after ring closure to form a compound of formula (V). A procedure for carrying out this conversion is described in Speciality Chemicals Magazine, April 2003, page 36-38.

Z groups which may be converted to dimethylaminomethyl are groups such as –CH_2-L, -CH_2-NO_2, -MgHal, cyano, aldehyde, -CH_2-O-Pg, -CH_2-NPg_1Pg_2, -CH_2-$NMePg_1$, -CH_2-$NHCH_3$, -CH_2-NH_2, -CO-$N(CH_3)_2$, -$CH(A^1R^{12})(A^1R^{13})$, -$(A^1R^{14})(A^2R^{15})(A^3R^{16})$, -$COOR^{17}$, -$CH_2$-CO-$NH_2$, -CH=CH-$R^{18}$ or –$CONHR^{19}$, wherein Pg is a protection group for an alcohol group, Pg_1 and Pg_2 are protection groups for an amino group, R^{12} and R^{13} are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and optionally alkyl substituted aryl or aralkyl groups or R^{12} and R^{13} together form a chain of 2 to 4 carbon atoms, each of R^{14} - R^{18} are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, 2_{1-6} alkynyl and optionally C_{1-6} alkyl substituted aryl or aryl-C_{1-6} alkyl, R^{19} is hydrogen or methyl and A^1, A^2 and A^3 are selected form O and S; L is a leaving group, such as halogen or -O-SO_2-A wherein A is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or optionally C_{1-6} alkyl substituted aryl or aryl-C_{1-6} alkyl.

Compounds wherein Z is -CH_2-O-Pg may be converted to the corresponding compounds wherein Z is dimethylaminomethyl as described in WO 01/43525, WO 01/51478 or WO 01/68631 or by analogous methods.

Compounds wherein Z is -CH_2-L, wherein L is a leaving group, may be converted to a dimethylaminomethyl group in the same manner.

Compounds wherein Z is -CO-$N(CH_3)_2$ and -CO-NHR^{19}, wherein R^{19} is hydrogen or methyl, may be converted to the corresponding compounds wherein Z is dimethylaminomethyl as described in WO 01/43525 or WO 01/68631 or by analogous methods.

Compounds wherein Z is -CH_2-$NMe(Pg_1)$ or -CH_2-N(Pg1)(Pg2) may be converted to the corresponding compound wherein Z is dimethylaminomethyl as described in WO 01/43525 or WO 01/68631 or by analogous methods.

Compounds wherein Z is -$CH(A^1R^{12})(A^2R^{13})$ may be converted to the corresponding compounds wherein Z is as described in WO 01/43525 or WO 01/68631 or by analogous methods.

Compounds wherein Z is -C(A^1R^{14})(A^2R^{15})(A^3R^{16}) may be converted to the corresponding compounds wherein Z is dimethylaminomethyl as described in WO 01/68631 or by analogous methods.

Compounds wherein Z is -$COOR^{17}$ may be converted to the corresponding compounds wherein Z is dimethylaminomethyl as described above, starting with the carboxylic acid ester.

Compounds wherein Z is –CH_2-$CONH_2$ may be converted to the corresponding compound wherein Z is as described in WO 01/43525 or WO 01/68631 or by analogous methods.

Compounds wherein Z is –CH=CHR^{18} may be converted to the corresponding compound wherein Z is dimethylaminomethyl as described in WO 01/43525 or WO 01/68631 or by analogous methods.

Compounds wherein Z is cyano or –CH_2-NO_2 may be converted to the corresponding compound wherein Z is dimethylaminomethyl as described in WO 01/68629 or by analogous methods.

Compounds wherein Z is –MgHal may be converted to the corresponding compound wherein Z is dimethylaminomethyl as described in WO 01/68629 or by analogous methods.

Preferably, Z is dimethylaminomethyl. If Z is not dimethylaminomethyl, conversion of Z to a dimethylaminomethyl group is suitably carried out after ring closure.

Compounds wherein the dotted line represents a double bond may be converted to the corresponding compound wherein the dotted line is a single bond by the methods described in WO 01/68630. Preferably the reduction is carried out after ring closure.

Experimentals

In the following examples % conversion and optical purity were measured and calculated as described below:

HPLC analysis condition (for conversion rate):
Column: A Lichrospher RP-8 column, 250 x 4 mm (5 μm particle size)

Eluent: Buffered MeOH/water prepared as follows: 1,1 ml Et_3N added to 150 ml water, 10% H_3PO_4(aq) is added to pH=7 and water is added to a total of 200 ml. The mixture is added to 1,8 L MeOH.

Temperature: 35°C
Flow rate: 1 mL/min
Pressure: 16,0 MPa
Detection: UV 254 nm
Injection volume: 10 microL

Conversion rate (%) = P/(S+P) x 100, (P: amount of product, S: amount of residual substrate).

Super critical fluid chromatogeaphy. Analysis condition (for optical purity):

Column: Daicel AD column with the dimensions 250 x 4,6 mm (5 μm particle size)
Mobile phase: Carbon dioxide
Modifier: Methanol with diethylamine (0.5%) and trifluoroacetic acid (0.5%).
Modifier gradient: 1-2% in 4 minutes
2-4% in 4 minutes
4-8% in 4 minutes
8-16% in 4minutes
16-32% in 4 minutes
32-45% in 1,62 minutes

Temperature: Ambient temperature
Flow rate: 2 mL/min
Pressure: 20 mPa
Detection: UV 230 nm and 254 nm
Injection volume: 10 microL

Optical purity (% ee) = (A-B) / (A+B) x 100, (A and B represent corresponding stereo isomer, A>B)

E-value = ln ((1-c/100) x (1-Es/100)) / ln ((1-c/100) x (1+Es/100))
(c: convertion ratio, Es: optical purity of residual substrate)

Example 1

(S)-1-(3-dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile hydrogen oxalate

To a mixture of 3,7 g S-citalopram diol and 6,3 g (R/S)-citalopram diol butyrate ester (R/S = 3:1) in 50 ml tetrahydrofuran was added 1,2 g (1,1 eq.) succinic anhydrid. Allowed to stir overnight at room temperature. Precipitated S-citalopram diol succinic ester was filtered off and washed with cold tetrahydrofuran to obtain 3,1 g ester 98% pure. Crystals were dried in oven and subsequently dissolved in 50 ml anhydrous dimethylformamide. To the solution was added 1,1 g NaH (60% suspension in oil) and stirred overnight at room temperature. The mixture was quenched with water and extracted with 3 times 50 ml diethylether. The combined organic phases were washed with 50 ml water and dried with Na_2SO_4 and evaporated in vacuo. The remaining oil was dissolved in 14 ml acetone and 630 mg oxalic acid was added. After 1h stirring at room temperature, the precipitated crystals were filtered off and washed with cold acetone to obtain 2,02 g escitalopram oxalate (ee-value 95%)

Example 2

(Preparation of the mixture used in example 1)

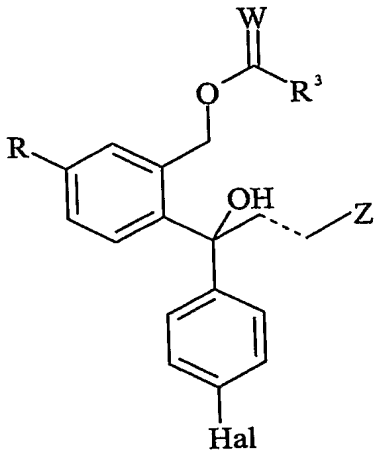
(S)-4-[4-Dimethylamino-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-hydroxymethyl-benzonitrile

To a stirred solution of racemic 4-[4-Dimethylamino-1-(4-fluoro-phenyl)-1-hydroxy-butyl]-3-hydroxymethyl-benzonitrile (29 mmol, 10 g) and vinylbutyrate (58 mmol, 7,5 ml) in anhydrous 1,4-dioxane (142,5 ml) is added lipoprotein lipase pseudomonas sp. (160 U, 250 mg). The reaction is heated to 50 °C and followed by HPLC. After 192 hours at a conversion of 41%, additional 250 mg lipase was added. After 504 hours, at a conversion of 63 % the reaction was stopped. The enzyme is

filtered off and washed with a small amount of 1,4-dioxane. The combined organic phases are evaporated *in vacuo* and subsequently analyzed on super critical fluid chromatography. Obtained EE-value ((S-diol) = 95% (S-diol/R-diol = 40:1).

Claims:

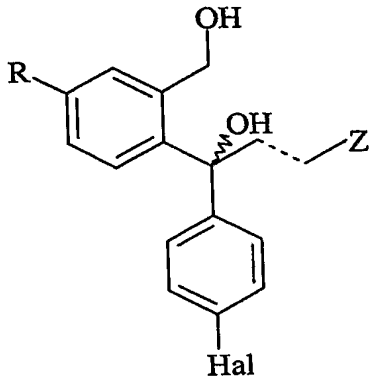
1. A method for the isolation and purification of the compound having a formula



(IV)

wherein R is cyano or a group which may be converted to a cyano group, the dotted line represents a double or single bond, Hal is halogen, Z is a dimethylaminomethyl group or Z is a group which may be converted to a dimethylaminomethyl group, W is O or S and R^3 is -Y-R^1 wherein Y is a bond, O, S or NH and R^1 is C_{1-10}-alkyl, C_{2-10}-alkenyl or C_{2-10}-alkynyl all of which may optionally be substituted with one or more substituents selected from C_{1-10}-alkoxy, C_{1-10}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-10}-alkylamino, di-(C_{1-10}-alkyl)amino, aryl, aryloxy, arylthio and heteroaryl, or R^1 is aryl, wherein any of the the aryl and heteroaryl groups may optionally be substituted one or more times with substituents selected from C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{2-10}-alkynyl, C_{1-10}-alkoxy, C_{1-10}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-10}-alkylamino and di-(C_{1-10}-alkyl)amino, or a salt thereof

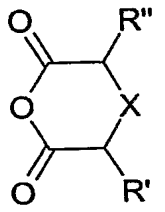
and/or a diol of formula



(II)

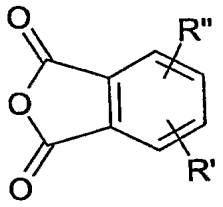
wherein R, Z, Hal and the dotted line are as defined above, or a salt thereof, from a mixture containing the compound of formula (IV) and the diol of formula (II), which comprises:

a) reacting said mixture containing the compound of formula (IV) and the diol of formula (II) with a cyclic anhydride or imide of formula



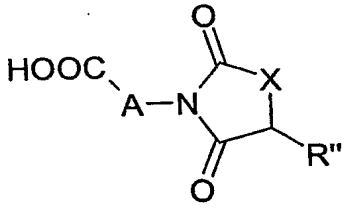
(Ia)

or



(Ib)

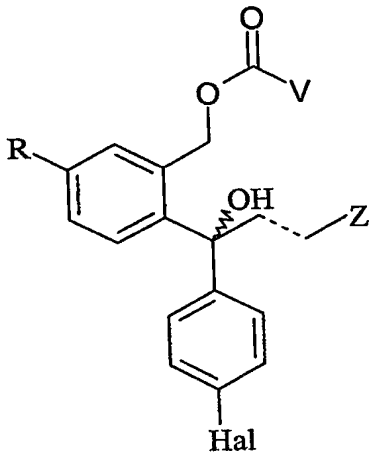
or



(Ic)

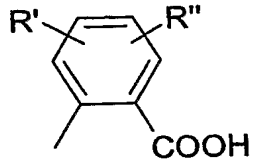
wherein X is $-(CHR'''')_n-$, wherein n is 0-2; and R', R" and R'''' are independently selected from hydrogen or C_{1-6}-alkyl, and A is C_{1-6}-alkylen, phenylen, or naphthylen wherein the C_{1-6}-alkylen, phenylen, or naphthylen groups may optionally be substituted with one or more times with C_{1-6}-alkyl;

to form a mixture of the compound of formula (IV) and an ester having the formula



(V)

wherein R, Z and Hal is as defined above and V is –CHR'-X-CR''-COOH, -X-CHR''-CO- NH-A-COOH, - CHR''-X-CO-NH-A-COOH or



wherein R', R'', X and A are as defined above;

b) allowing the acid of formula (V) to precipitate from the reaction mixture; and

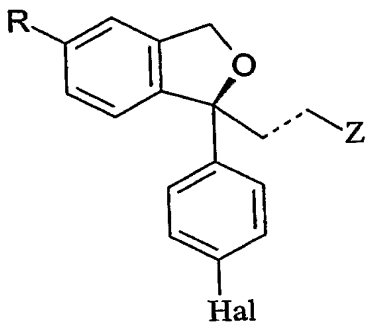
c) separating the precipitate of the compound of formula (V) from the reaction mixture, optionally followed by isolation of the compound of formula (IV) or a salt thereof from the reaction mixture.

2. The method according to claim 1 wherein the S-enantiomer of the compound of formula (V) is separated from the R-enantiomer of the acyl derivatitive of formula (IV).

3. The method according to claim 1 wherein the S-enantiomer of the acyl derivative of formula (IV) is separated from the R-enantiomer of the compound of formula (V).

4. The method according to claim 2 wherein the R group in the compound of formula (V) in obtained in the form of the S-enantiomer is optionally converted to cyano, the Z group in the compound of formula V obtained is optionally converted to a dimethylaminomethyl group, Hal is

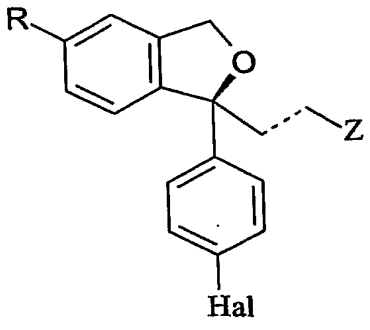
optionally converted to fluoro and /or a dotted line representing a double bond is optionally converted to a single bond, in either order, followed by conversion of the compound of formula (V) to escitalopram or a derivative thereof having the formula



(VI)

wherein R, Z and Hal is as defined above by treatment with a base, optiona optionally followed by, in either order, conversion of the group R to a cyano group, conversion of the group Z to a dimethylaminomethyl group, conversion of Hal to fluoro, and conversion of a dotted line representing a double bond to a single bond; optionally followed by conversion of escitalopram or a derivative of formula (VI) to a salt thereof.

5. The method according to claim 3 wherein the R group in the compound of formula (IV) the obtained in the form of the S-enantiomer is optionally converted to cyano, the Z group in the compound of formula IV obtained is optionally converted to a dimethylaminomethyl group, Hal is optionally converted to fluoro and /or a dotted line representing a double bond is optionally converted to a single bond, in either order, followed by conversion of the compound of formula (IV) to escitalopram or a derivative thereof



(VI)

wherein R, Z and Hal is as defined above by treatment with a base, optionally followed by, in either order, conversion of the group R to a cyano group, conversion of the group Z to a dimethylaminomethyl group, conversion of Hal to fluoro, and conversion of a dotted line

representing a double bond to a single bond; optionally followed by conversion of escitalopram or a derivative of formula (VI) to a salt thereof.

6. The method according to any of claims 4 or 5 wherein the basic ringclosure is carried out by treatment with with a base such as $KOC(CH_3)_3$ and other alkoxides, NaH and other hydrides, triethylamine, ethyldiisopropylamine or pyridine.

7. The method according to any of claims 1-6 wherein Hal is fluoro and R is halogen or cyano, preferred R is cyano.

8. The method according to any of claims 1-7 wherein the dotted line represents a single bond.

9. The method according to any of claims 1-8 wherein and Z is dimethylaminomethyl or a group that may be converted to a dimethylaminomethyl group, preferred Z is a dimethylaminomethyl group.

10. The method according to claims 1-9 wherein the anhydride is a compound of formula (Ia).

11. The method according to claim 10 wherein the anhydride is succinic anhydride or glutaric anhydride.

12. The method according to claims 1-9 wherein the anhydride is a compound of formula (Ib).

13. The method according to claim 12 wherein the anhydride is phtalic acid anhydride.

14. The method according to claims 1-9 wherein the reagent is an imide is a compound of Formula (Ic).

15. The method according to claim 14 wherein the imide is N-phenyl-succinimide substituted in the phenyl ring with a carboxy group.

16. The method according to any of claims 1-15 wherein Y in the compound of formula (IV) is a bond.

17. The method according to any of claims 1-15 wherein Y in the compound of formula (IV) is O or S.

18. The method according to claim 17 wherein Y in the compound of formula (IV) is O.

19. The method according to any of claims 1 –15 wherein Y in the compound of formula (IV) is NH.

20. The method according to any of claims 16-19 wherein R^1 is selected from C_{1-4}-alkyl, C_{2-4}-alkenyl and C_{2-4}-alkynyl all of which may optionally be substituted one or more times with substituents selected from C_{1-4}-alkoxy, C_{1-4}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-4}-alkylamino and di-(C_{1-4}-alkyl)amino.

21. The method according to claim 20 wherein R^1 is selected from C_{1-3}-alkyl, C_{2-3}-alkenyl and C_{2-3}-alkynyl all of which may optionally be substituted one or more times with substituents selected from C_{1-3}-alkoxy, C_{1-3}-alkylthio, hydroxy, halogen, amino, nitro, cyano, C_{1-3}-alkylamino and di-(C_{1-3}-alkyl)amino.

22. The method according to claim 20 wherein R^1 is C_{1-4}-alkyl.

23. The method according to claim 21 wherein R^1 is C_{1-3}-alkyl.

24. The method of claim 23 wherein R^1 is methyl, ethyl or propyl, preferably propyl.

25. The method according to any of claims 1-24 wherein the mixture of a compound of formula (II) and (IV) is prepared by selective enzymatic acylation or selective enzymatic deacylation.

Abstract

The invention relates to a method of separating and isolating obtain an acylated derivative of S-diol by reaction of a mixture the diol and an acylated derivative thereof with a compound which form a derivative of the diol containing a carboxylic acid group. The acylated derivative containing a carboxylic acid group precipitates once it is formed and may easily be separated from the reaction mixture.

Application Data Sheet

Application Information

Application Type::	Provisional
Subject Matter::	Utility
Suggested Group Art Unit::	N/A
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	METHOD FOR THE PREPARATION OF INTERMEDIATES WHICH MAY BE USED FOR THE PREPARATION OF ESCITALOPRAM
Attorney Docket Number::	05432/0200888-US0
Request for Early Publication?::	No
Request for Non-Publication?::	No
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Denmark
Status::	Full Capacity
Given Name::	Lars
Middle Name::	Ole
Family Name::	Lyngso
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Country of Residence::	Denmark
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Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880

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